

Financial conflicts of interest in psychiatry

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The issue of conflicts of interest has brought clinical medicine to an unprecedented crisis of credibility. The situation of psychiatry does not appear to be different from other areas of medicine. The problems caused by the increasing financial ties between the pharmaceutical industry and researchers and clinicians can be addressed only by a complex effort encompassing both the establishment of lines of support of independent researchers who are free of substantial conflicts of interest and better disclosure policies and conduct regulations as to financial ties. Such effort requires a bold shift from current, largely inadequate strategies. In the long run it may entail, however, substantial advantages to patients, clinicians, researchers, the health industry and the civil society at large. Psychiatry, in view of its humanistic and social roots, may lead this effort.

Key words: Conflicts of interest, disclosure, psychotropic drugs, practice guidelines, psychiatry

(*World Psychiatry* 2007;6:19-24)

The proliferating connections between physicians and the pharmaceutical industry have brought the credibility of clinical medicine to an unprecedented crisis (1). The public seems to be increasingly skeptical of clinical medicine, since corporate actions that have placed profit over public health have become regular news in the media (2). Medical journals have been defined by a former editor as “an extension of the marketing arm of pharmaceutical companies” (3). The dangers of medicine’s complicity with big business have been disclosed to the lay public in several books (4-7). In one of these books, John Abramson admirably unveils how propaganda has substituted research evidence in the medical field (7).

More and more voices from academic medicine are questioning the relationship between the pharmaceutical industry and the physicians (8). Conflicts of interest have thus become a major issue of concern in medicine, including psychiatry, and are getting more and more important for medical journals (9). They undermine the credibility of papers which are submitted, their review process, and even the editorial decisions about acceptance or rejection.

The notion of conflict of interest is widely used but may entail different meanings. Margolis (10) distinguishes between conflicting interests and conflicts of interest. The former occur in any situation where competing considera-

tions are presumed to be legitimate. Conflicts of interest, on the other hand, are characterized by individual occupying dual roles which should not be performed simultaneously. Because of the potential for abuse, performing both roles at the same time is considered to be inappropriate. Which roles? For instance, being a researcher and holding a financial interest in an area related to the research one is involved in. Table 1 lists the main sources of conflicts of interest.

I will describe some of the insights that research on conflicts of interest has generated in medicine and psychiatry, and some strategies which may counteract this phenomenon.

CONFLICTS OF INTEREST IN MEDICINE

In the past decade there has been a

Table 1 Main sources of conflicts of interest in medicine

Being a clinician/researcher and:
- an employee of a private firm
- a stockholder
- a member of a company board of directors
- a regular consultant of a private firm
- an occasional consultant of a private firm
- an official speaker of a private firm
- an occasional speaker of a private firm
- getting refunds from a private firm
- recipient of honoraria
- a clinical investigator in a sponsored trial
- recipient of research support from a private firm
- owing a patent

considerable amount of research, mostly in the US, on the issue of conflicts of interest in medicine. This research has yielded important insights into the dimensions and importance of the phenomenon. Special attention will be given to the psychiatric field.

Prevalence is very high

The first idea of the prevalence of situations of conflict of interest in scientific research came from a landmark study which appeared in the 1990s. Krimsky et al (11) analyzed 789 articles written by authors from Massachusetts universities publishing in leading scientific journals in 1992. In one out of three cases, at least one author had a vested interest in research. Krimsky et al (11) took a very conservative stand as to what constitutes a financial conflict of interest: owing a patent directly related to the published work; being a major stockholder or executive in a company with commercial interests tied to the research, or serving on the board of directors of such a company. The percentage of cases of conflict of interest would have greatly increased if consultancies and honoraria had been taken into account. The study clearly showed the extent of corporate presence in scientific publishing. These results, however, were systematically downplayed by the scientific community, as exemplified by the

response of *Nature* to them (11).

The same group of researchers addressed the issue of the financial ties with the pharmaceutical industry of the 170 DSM-IV panel members. Ninety-five (56%) had one or more associations with companies (12). The percentage reached 100% among members of the panels on mood disorders and schizophrenia and was above 80% among members of the panels on anxiety and eating disorders (12).

It has been reported (8) that one of ten US physicians is currently engaged in a formal consultancy with investment industry. We should expect this proportion to be much higher in clinical research, including psychiatry, even though there may be differences from one field to another.

Disclosure is seldom performed

Disclosure has emerged as a first and essential step for dealing with conflict of interest contamination in science. But, despite journals' policies, it is seldom performed (in less than 1% of medical articles according to a study by Krinsky (13)). Such disclosure often takes place in the media, instead of coming from the authors or scientific community. For instance, Zalewski (14) illustrates an impressive list of examples where the problem of conflict of interest was associated with important scientific and clinical issues. At times, conflicts of interest may undermine the credibility of scientific data, such as in the scandal over a study on a heart attack medication (tissue plasminogen activator, TPA) published in the *JAMA*, when a reporter from *Newsday* revealed that at least 13 researchers were long-term stockholders of the company manufacturing the drug.

Such scandals have also involved psychiatric researchers (4). A very recent one about an article on vagus nerve stimulation has led to the resignation of the lead author from the editorship of an important journal (15). It is worth mentioning that this scandal was not triggered by an investigative reporter, but by a member of the society which was linked to the journal.

It must be noted that, while disclosure has become standard practice in North American meetings and journals, it has not achieved wide currency in Europe.

Scientific societies may be beholden to the drug industry

Glassman et al (16) investigated whether revenues generated from pharmaceutical advertisements in medical journals create potential conflicts of interest for nonprofit physician organizations that own those journals. They found that financial conflicts of interest were substantial, and some prestigious medical organizations, such as those underlying the *JAMA* and the *New England Journal of Medicine*, could be viewed as beholden to the drug industry. In an accompanying editorial, Lexchin (17) reported on the growing concern about the relationship between the World Health Organization (WHO) and the pharmaceutical industry. The WHO issued a set of guidelines for the diagnosis and management of essential hypertension in conjunction with the International Society of Hypertension. A letter signed by close to 900 physicians and scientists pointed out that the guidelines ignored ground rules of clinical assessment and placed an excessive weight on trials funded by the pharmaceutical companies. This casts serious doubts on the WHO, which has been accepting temporary substitutes of personnel from the pharmaceutical industry. As has been pointed out concerning the diagnosis of depression and the use of antidepressant drugs, the game is clear: to get as close as possible to universal consumption of a drug, either by stretching its indications (e.g., to include demoralization) or by encouraging its preventive use (18). Scientific societies may control medical journals and affect editorial policies and the selection of papers. Further, financial ties may also affect the scientific meetings of those societies. This is something anyone walking in a major society meeting may easily perceive.

Authors of clinical practice guidelines are often linked to the pharmaceutical industry

Choudhry et al (19) examined authors of clinical practice guidelines endorsed by North American and European societies on common adult diseases. Eighty-seven percent of authors had some form of interaction with the pharmaceutical industry (58% had received financial support to perform research and 38% had served as employees or consultants for a pharmaceutical company). In published versions of the 44 clinical practice guidelines, specific declarations regarding the personal financial interactions of individual authors with the pharmaceutical industry were made in only two cases (19).

Attending drug sponsored scientific events is associated with an increased prescription of the sponsor's medication

A review (20) has outlined how attending sponsored continuing medical education (CME) events and accepting funding for travel or lodging for educational symposia were associated with an increased prescription rate of the sponsor's medication. Attending presentations given by pharmaceutical representative speakers was also associated with nonrational prescribing. Wilkes (21) commented on the consequences of the interactions: "Physicians take gifts from drug companies and then spend patients' money to help make the same pharmaceutical industry the most profitable in the world. They recruit 'research' subjects without advising them of the personal financial gain that accrues to them.... All these behaviors are directly opposed to what patients and society expect from us in return for the privileges that have been bestowed". And, as the subtitle of the editorial indicates, when trust goes, so does the healing power of physicians.

Studies sponsored by pharmaceutical companies are more likely to have outcomes favorable to the sponsor

It has been repeatedly reported that studies sponsored by pharmaceutical companies are more likely to have outcomes favorable to the sponsor (22-25). Industry sponsorship also results in restrictions on publication and data sharing (23) and in selective reporting (26). Perlis et al (25) examined funding sources and authors' financial conflicts of interest in clinical trials published in four leading American journals concerned with psychiatry. Sixty percent were funded by a pharmaceutical industry, and conflict of interest was associated with a greater likelihood of reporting a drug to be superior to placebo. Further, Melander et al (26) analyzed controlled studies of selective serotonin reuptake inhibitors and found that sponsored studies with favorable results were more often published than negative studies. A very good example of this selective publication is given by the scandal following the finding that a major pharmaceutical company allegedly withheld from the medical community clinical trial findings which indicated that a widely used antidepressant had no beneficial effect in treating adolescents (27). This casts serious doubts on the representativeness of the drug trials which are included in meta-analyses (28). Further, even systematic reviews require careful critical appraisal (29,30). Conflicts of interest may affect this appraisal. Evidence-based medicine may thus be a deceptive instrument of propaganda.

Heres at al (31) analyzed the sources of bias which may limit the validity of head-to-head comparison studies of second-generation antipsychotics, such as equivalent dosages, study entry criteria, statistical analysis, reporting of results and wording of findings.

Often researchers do not own their data

Mello et al (32) explored the legal agreements that exist between industry sponsors and academic investigators.

In 80% of institutions the sponsor may own the data and in 50% the sponsor may write up the results for publication. There have been many instances in the media about the struggles between clinical researchers and pharmaceutical companies as to the publication and analysis of data (14). In most of the instances investigators have been quite alone in their battles. In sponsored scientific presentations at meetings, it is a quite common practice that the slides of speakers are reviewed and approved by the sponsor.

Independent investigators are a threat to special interest groups

There have been growing concerns about the independence of academic psychiatry (33). We are often led to believe that virtually all clinical investigators should have some ties with the pharmaceutical industry, even though this is not true (8). We are also led to believe that the advertising section of a major medical journal has nothing to do with the editorial section. There is evidence to call such view in question (34). Apparently, it is also possible to buy editorials (35).

When the percentage of investigators with conflicts of interest reaches 100% (as in DSM panels), this means that there is systematic exclusion of independent investigators. They may represent a threat to special interest groups, self-selecting academic oligarchies who are the gatekeepers of corporate interest in scientific information (36). Several examples are available to indicate the degree of retaliation that may be provided to outliers (36).

WHAT CAN WE DO?

So far, the problem of conflicts of interest in medicine has been conceptualized in naïve terms. The scenario is pictured as the corporate industry (bad guys) exerting more and more pressure on physicians (helpless victims), with the medical journals (good guys) attempting to protect both the physicians

and their patients. The inadequacy of this scenario is reflected by the pathetic outcomes of the efforts to limit the phenomenon. For instance, the *JAMA* rules for reporting industry-sponsored studies require that at least one author, who should not be a firm employee, takes full responsibility for the integrity of the data and that an independent biostatistician should perform or confirm data analysis (37). Does an academic researcher loaded with conflict of interest provide more trust than a firm employee? I believe the contrary is true. Similarly, registration of trials and tougher standard for disclosure are certainly welcome (38), but comprehensive disclosure could not restore public trust as wished.

A crucial problem lies in the lack of a definition of substantial conflict of interest. Are eating a pizza at a drug-sponsored lunch and being a regular consultant to a firm the same thing? Table 2 outlines some tentative criteria which are based on Krinsky et al's work (11). The first two situations shown in the Table 2 involve the concept of continuity of a relationship with a private firm. Indeed, occasional consultancies, grants for performing an investigation, or receiving honoraria or refunds in specific occasions would not be a source of substantial conflict of interest. The latter two situations depicted in the Table 2 indicate major financial sources of bias.

Another issue is that the problem of conflicts of interest has been viewed so far mainly in negative terms: how to limit corporate influence in medical research. There has been little or no emphasis on the fact that the scientific community is draining itself of a reservoir of disinterested experts who can be called upon to advise government poli-

Table 2 Criteria for the presence of substantial conflict of interest of a researcher

The researcher meets at least one of the following:
- Being an employee of a private firm
- Being a regular consultant or in the board of directors of a firm
- Being a stockholder of a firm related to the field of research
- Owning a patent directly related to the published work

cy makers and physicians on the safety and efficacy of treatments, on the hazard of chemicals and on the safety of technology (4). Do we believe that researchers who opted for not having any form of conflict of interest and, by doing this, gave up financial gains, are of special value? Or do we believe that their opinion is in no way different from that of researchers with substantial conflicts of interest and that they are simply a pathetic remnant of the past century? Is the pharmaceutical industry interested in researchers who may cooperate with marketing, as most of the academic physicians who are involved with them now do, or are they interested in independent and critical minds? Not surprisingly, innovative and groundbreaking development of new drugs by the pharmaceutical industry has been extremely disappointing in the past few years (5).

Yet, the experts who are free of conflicts of interest may find increasing difficulties in obtaining appropriate visibility at meetings and in journals and in getting support for their research. It is not that disinterested experts are extinct: it is that they are marginalized by the gatekeepers of corporate interest within public institutions, scientific societies and medical journals.

As a result, if we believe in the value of independent research and researchers and in the need of preserving and promoting this independence, we should endorse the steps which are outlined in Table 3. If a grant agency committee, or a medical journal, or a scientific meeting committee does not include experts with no substantial conflicts of interest, and particularly those who have none, it does not deserve credibility.

For certain positions (e.g., editor-in-chief of a medical journal), the situation should be evaluated on an individual basis. For instance, tie to a single firm, contrary to what is often assumed, allows an easy monitoring of an editor's job (he or she can be excluded from assessing papers dealing with products of that firm), whereas multiple forms of conflict of interest make this control impossible. At times advertising departments appear to influence editorial de-

cisions in journals which advertise drugs or devices (39). Such influence may be particularly strong if the editor is vulnerable because of his/her conflict of interest.

Information overload is the key vehicle of pharmaceutical propaganda (40). A psychiatrist may be overwhelmed by scientific articles, often of redundant nature. He or she may become aware of certain articles because of firms pointing to those, or because they appear in very well-known and distributed journals. Yet this may be very misleading. Conflict-free articles (particularly review papers) and purely subscription-based journals should become the focus of attention of clinicians who have become educated to the issue of conflicts of interest (40).

Only in this context, interventions aimed to getting a better control of conflicts of interest may become successful (Table 4). While disclosure has become standard practice in North American meetings and journals, it is still poorly practiced in Europe. It should be emphasized that in psychiatry conflicts of interest may arise not only when there are ties with the pharmaceutical industry, but also when the researchers, for instance, are involved in private schools for training in psychotherapy. Disclosure is the minimal requirement for scientific credibility. It should have a specific time frame (e.g., 3 years). When an endless list of financial ties is provided,

it should be clear that it becomes virtually meaningless, unless the potential implications of such ties are described in a note.

Each scientific organization should have a conflict of interest advisory committee that represents different segments of the organization and that should be a referral point to individual members identifying possible conflicts of interest (41). Scientific organizations may also request disengagement from corporations that abuse public trust (e.g., false advertising, regulatory fines) and do not allow publication of scientific results (42). Individual members of a society can also decline participation in specific meetings or society events (43), or refuse to pay the dues of the society, or write to the journal which was involved in a specific case of conflict of interest (and the letter should be published, whereas this is seldom done with the excuse of lack of space or by not having a dangerous letter section). Members attending a meeting of their association should be able to rate the quality and the influence of the pharmaceutical industry with appropriate evaluation forms and to manifest their dissent (electronic mail is a powerful instrument for it).

The development of specific policies for integrity of agencies and pharmaceutical industries is also important. The American College of Cardiology Foundation and the American Heart Associ-

Table 3 Lines of support to independent researchers who are free of substantial conflicts of interest

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- Priority for obtaining grants from public agencies supported by taxpayer money
 - Priority for scientific societies and medical journals editorship positions
 - Adequate visibility in scientific societies meetings programs
 - Inclusion only of researchers with no substantial conflict of interest in clinical practice guidelines groups
 - Conflict-free investigations and reviews should be emphasized in training and continuing medical education and should have priority in medical journals
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Table 4 Steps to addressing financial conflicts of interest in medical research

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- Disclosure should become the rule in all scientific meetings and journals
 - Each scientific organization should have a conflict of interest advisory committee
 - Individual members of societies and readers of medical journals should express their dissent from presentations and articles biased by conflict of interest
 - Specific policies for integrity in science by professional societies, universities, granting agencies, pharmaceutical companies
 - Independent review bodies (within each field) for examining the issues concerning conflicts of interest
 - Educational plans for recognizing conflicts of interest
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ation's report on professionalism and ethics (44) may inspire psychiatric associations to take similar steps.

The creation of independent review bodies (within each field) for examining the issues concerning conflicts of interest would be another important step. Such bodies might provide peer support to struggling authors or editors, well beyond the generic, if not ridiculous, encouragement to register unpublished research (45). Further, these bodies may become an important reference to consumers' associations, which so far have not fully realized the importance of addressing the issue of conflicts of interest. A notable exception is represented by the brave battle of a British consumers' association for the recognition of withdrawal reactions following use of benzodiazepines (46) and second-generation antidepressants (47). We should realize that public research money is often invested for the benefit of special interest groups instead of addressing key public health issues.

Finally, professional training programs (e.g., medical school, residency training, etc.) should teach individuals to recognize conflict of interest situations (41) and increase awareness of biased interpretations of research results (28).

CONCLUSIONS

The problem of conflicts of interest in psychiatry does not appear to be different from other fields of clinical medicine. It can be addressed only by a complex effort on different levels, which cannot be postponed any longer. In fact, either clinical researchers become salespeople (and the main aim of many scientific meetings today is apparently to sell the participant to the sponsor) or they must set out boldly to protect the community from unnecessary risks (36). By choosing the latter course, they should be aware that they will also be defending their own intellectual freedom (48). Psychiatry, in view of its humanistic and social roots, may lead this effort.

Disclosure

The author has received grant support for his studies from the Italian Ministry of Education, University and Research, the Italian National Research Council, the Italian National Institute of Health and the Carisbo Foundation. He is editor-in-chief of *Psychotherapy and Psychosomatics* (Karger, Basel).

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